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# A Pragmatic Approach to Immunity & Respiratory Viral Infections

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My paternal grandmother was notorious in our family for having succinct and poignant pearls of wisdom. One that was used a lot under stressful times was, "You play the cards in your dealt in life to the best of your abilities." During these unprecedented, turbulent times in our modern world, these sagacious words ring even more true.

We are unfortunately living in a time when SARS-CoV-2, more colloquially known as COVID-19 (corona virus disease 2019) is as pervasive on everyone's mind and in the media, as the necessity it is to drink water in order to survive. Our stressful times are now exacerbated by riots, civil unrest, political and economic uncertainties.

What we're experiencing as a nation and as a world has not been seen in generations. It seems to affect everyone differently, physical, emotionally, and spiritually. I have family, friends, colleagues, and patients, for whom it's just another day, and I have ones that are on the complete other side of the spectrum, feeling so distraught, they will descend into madness; and everything in between.

In just the past few months since the pandemic really seemed to grip the world, the research literature has exploded into thousands of articles. I won't even go into everything else: blogs, tweets, posts, videos, etc., as it's mindboggling and many times nauseating. Everyone seems to have an opinion, whether based on sound logic and science or not.

At first, I was going to write an article on the history of SARS-CoV-2, as well as pathophysiology, pathogenesis, testing, clinical symptoms, and naturopathic therapeutic interventions.

I have decided not to approach this article via this manner, given that there are so many sources out there that have done an outstanding job. For example, I cannot emphasis enough how readers should read *IMCJ*'s Focus on COVI-19, Vol 19, No. S1. It is exceptionally thorough and very well done.

So, why should I write what already has been written, albeit some of the following may be a bit redundant of other outstanding articles? Instead, I will write about the most common viruses that cause respiratory disorders, and what naturopathic treatment interventions have been proven in the scientific literature (evidence-based) to be effective in both prevention and treatment of many viruses, regardless of type. There are too many interventions to list, so I will focus on the ones I have utilized in my private practice for the past ten years (clinical-based medicine). I will provide a brief overview of SARS-CoV-2 virology, along with epidemiology. I will also discuss interventions to mitigate cytokine storm and attenuate inflammation, outside the use of acetaminophen and NSAIDS.

Lastly, there is a fact that I feel has been significantly neglected the past few months since the pandemic really gained so much momentum, and that is the emotional impact. I will discuss some "natural" therapies that have proven efficacy in what many are seeing in not only our patients, but friends, families, colleagues and maybe even ourselves—anxiety, depression and even despair.

## Coronavirus Context

According to *Nature Reviews Microbiology*, there are more than $1 \times 10^{31}$ (10 quintillion, or in the US, nonillion) viruses on Earth,[1] but only a bit more than 200 are capable of causing human illness.[2] The human microbiome contains approximately 38 trillion bacteria.[3] Compare this to the human virome, which contains approximately 380 trillion viruses![4] Viruses are some of the smallest creatures on Earth, between 20-400 nanometers (nm) in diameter. They are essentially packets of nucleic acids (either RNA or DNA), surround by a protein shell and sometimes lipids. They are dormant outside a living cell and they need to hijack a host's metabolic machinery in order to survive and produce copies of itself.[5,6]

According to the Centers for Disease Control (CDC), colds and flus occur all year, but the "season" for them is typically December through February.[7,8] Viral infections most commonly cause upper respiratory tract infections (URTI's), of which the most common are caused by influenza A and B, H5N1 and H7N9 avian influenza A, parainfluenza 1 through 4, adenoviruses, respiratory syncytial virus A and B and human metapneumovirus, rhinoviruses and yes, coronaviruses.[9]

Given the current times, I would like to focus on coronaviruses. These are zoonotic pathogens of enveloped RNA viruses that cause respiratory illnesses of varying severity from the common cold to fatal pneumonia and only seven are known to cause disease in humans. Four out of the seven most frequently cause symptoms of the common cold; coronaviruses 229E and OC43 are known to cause the common cold. Serotypes NL63 and HUK1 have also been associated with the common cold. Rarely,

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severe lower respiratory tract infections, including pneumonia, can occur, primarily in infants, older people, and the immunocompromised.[10]

## Epidemiology, Pathogenesis and Testing

As of August 21, 2020, there have been 22 773 308 *confirmed* global cases of COVID-19, with 795 196 deaths. In the United States, there have been 5,600,107 cases and 174 647 deaths (case fatality rate of 3.12%).[11] I emphasize confirmed because many countries may be underreporting cases and/or deaths.[12] Some countries, like North Korea, refuse to even report data to the World Health Organization (WHO).[13]

Viral shedding and the period of greatest infectiousness seems to be earlier in the stages of illness, when viral RNA levels in respiratory droplets are highest.[14] Is this person asymptomatic (does not have symptoms but is infected and will never develop symptoms), or pre-symptomatic (the phase when an individual is infected and may be shedding virus but hasn't yet developed symptoms), and can one tell the difference? No, since symptoms may show up between 2 to 14 days after exposure, with infectiousness starting about 2 days prior to symptom onset, peaking about 0.7 days before symptom onset, then declines within seven days, but can occur up to 21 days after exposure This is where nucleic acid amplification (NAAT), most commonly with reverse-transcription polymerase chain reaction (RT-PCR) tests can be valuable, since they can detect the viruses about a week before any symptoms even show up.[15,16,17]

Serological testing (IgA, IgM and IgG) seem to be a more precise diagnostic tool after day 14 of symptom onset, with IgA and IgM titers tending to dissipate after 3 weeks, while IgG confers long-term immunity, approaching 100% seropositivity by 16 to 20 days.[18,19] Recently, The Infectious Diseases Society of America (IDSA) released a statement stating that 3 to 4 weeks after exposure, is optimal.[20]

It should be noted that these are "general" statistics, in that antibody produced with SARS-CoV-2 are predicated upon how seriously ill the individual (i.e., less severe disease has been shown to lead to smaller antibody production[21]) became and underlying immune competence. Given this novel virus, we also don't know how long a person will have protective antibodies. One study showed IgG levels declining by a median of approximately 75 percent from the acute to early convalescent phase of illness, and at eight weeks following infection, 40 percent of asymptomatic patients and 13 percent of symptomatic patients did not have detectable IgG.[22]

According to a recent CDC report of over 370 000 confirmed COVID-19 cases in the US, the most common symptoms are cough in 50 percent, fever (subjective or >100.4°F/38°C) in 43 percent, myalgia in 36 percent, headache in 34 percent, and dyspnea in 29 percent. Anosmia, ageusia, abdominal pain, and rhinorrhea occur in less than 10% of cases.[23] Those infected with SARS-CoV-2 can have absolutely no symptoms, to mild, to severe and even death. Complications can be seen in the form of respiratory failure, arrhythmias, and thromboembolisms.[24] Certain lab values have now been associated with worse outcomes: elevations in D-dimer, ferritin, CRP, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), troponin, as well as lymphopenia and thrombocytopenia.[25,26,27]

Convalescence appears to be around two weeks for mild infections and three to six weeks for severe disease.[28] The most common persistent symptoms were fatigue (53 percent), dyspnea (43 percent), joint pain (27 percent), and chest pain (22 percent).[29] Recovery course is variable and depends on age and pre-existing comorbidities in addition to illness severity.

The immense details of the various common viral infections are beyond the scope of this article, but in this author's view, four main points should be considered: infection prevention, specific antiviral interventions, inflammation modulation, and immune balance and enhancement.

## Prevention

Benjamin Franklin coined the axiom, "an ounce of prevention is worth a pound of cure." This is especially apt today, particularly when it comes to infections. General strategies cannot be underscored enough. Diligent hand washing, use of hand sanitizer that contains at least 60% alcohol, respiratory hygiene (e.g., sneezing into elbow crease), avoiding touching the face, avoiding crowds and close contact with ill individuals, cleaning and disinfecting objects (bleach or at least 60% alcohol), surfaces that are frequently touched, wear a mask and stay at least 6 feet from other people who are not from your household in both indoor and outdoor spaces.[30,31]

Let us not kid ourselves, these are very stressful and trying times for everyone. Now, maybe more than we have ever experienced before in our lifetimes; ourselves and our patients need to be more cognizant of how stress and poor sleep negatively impacts our immune system. Chronic stressors are associated with suppression of both cellular and humoral response[32]and infection-fighting antibodies and cells are reduced during periods when you don't get enough sleep.[33]

Given the aforementioned statements, the diligent use of adaptogens and non-addictive sleep aids may provide tremendous benefits for the immune system, stress, anxiety and depression.[34] Botanical adaptogens like *Withania somnifera* (ashwagandha), *Glycyrrhiza glabra* (licorice) and *Rhodiola rosea* (rhodiola), have been used for thousands of years in Ayruvedic and Chinese medicines to help the body cope with stress, increase stamina and vitality, and also support the immune system.[35,36,37]

One of the added benefits of the use of adaptogens, is also the typical positive effect on the immune system. The withanolides and sitoindosides in ashwagandha

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cause a mobilization of macrophages, phagocytosis, and lysosomal enzymes.[38] The glycyrrhizin triterpene saponin may provide use in viral infections, particularly COVID-19 because it "binds angiotensin-converting enzyme II (ACE2), downregulates proinflammatory cytokines, inhibits the accumulation of intracellular reactive oxygen species (ROS), inhibits thrombin, inhibits the hyperproduction of airway exudates, and induces endogenous interferon."[39] Rhodiola contains over 30 compounds[40] including the most well studied being salidroside, rhodioloside and rosavin (exclusive to the rosea species)[41], increases B cells, T cells, NK cells, and cytokine facilitation.[42]

Melatonin's most famous use is as a sleep-aid, improving both sleep latency and quality of sleep,[43] but this revered hormone is also highly anti-inflammatory,[44] strong antioxidant[45], antiviral, showing efficacy in COVID-19 neurological sequelae[46] and immunomodulating.[47]

Simple interventions for which we have some of the greatest control over—diet and exercise—are often overlooked. What doesn't exercise do that is positive? It relieves stress, helps improve sleep quality and improves immune function.[48,49,50]

A healthy diet is the cornerstone of any aspect of proper immune function. Professor Philip Calder says it better than I: "Practically all forms of immunity are affected by protein-energy malnutrition, but non-specific defenses and cell-mediated immunity are most severely affected. Micronutrient deficiencies impair immune function … the gut-associated lymphoid tissue is especially important in health and well-being because of its close proximity to a large and diverse population of organisms in the gastrointestinal tract and its exposure to food constituents."[51]

Speaking of gut health, the human gastrointestinal (GI) microbiome has been well established to play an enormous role in human health, disease, immune function and inflammatory processes.[52,53,54] Ergo, the prudent use of prebiotics, probiotics, synbiotics and *Saccharomyces boulardii* can't be understated. Different strains supply different health aspects, but generally speaking all play vital roles in increasing sIgA, have anti-inflammatory properties, inhibit biofilm formation and are competitive inhibitors for opportunistic and yeast and bacteria.[55,56,57,58,59]

Then there is the world of immunobiotics. These are bacteria that either have been heat-shocked or have had their cell walls lysed and therefore are no longer alive. They promote systemic health through the mucosal immune system.[60] One strain in particular, *Lactobacillus plantarum* L-137 has a reasonable amount of human data showing that it activates IFN-γ and β, IL-12 (increasing the Th1 immune response), decreases upper respiratory tract infections, incidences, duration and severity, along with improving lung function.[61,62,63,64]

## Immune Support Nutrients

Vitamins A and D are critical for lymphocyte activation and proliferation, Th cell differentiation, tissue-specific lymphocyte homing, production of specific antibody isotypes, regulation of the immune response, increasing sIgA and the production cathelicidins (host defense peptides with antimicrobial and immunomodulatory functions).[65-69]

The cobalamin family (vitamin $B_{12}$) enhances natural killer (NK) cell activity, increases circulating lymphocytes and is immunomodulatory.[70,71] Probably the most well covered nutrient during the COVID-19 pandemic is vitamin C and it may well deserve its time in the spotlight. It is an antioxidant, stimulates NK activity and function, stimulates IL-2, stimulates conversion of naïve T helper cells to Th1 cells (required for host defense against intracellular viral and bacterial pathogens), stimulates T-lymphocyte activity, phagocyte function and leukocyte mobility.[72] Furthermore, it has been demonstrated in humans that during times of infection, ascorbate demands increase and when taken, shortens severity and duration of numerous infections.[73,74]

Selenium has been well studied and plays an important role in acute cellular immune response, particularly in viral and bacterial infections.[75] It is also a necessary cofactor of glutathione peroxidase, which is needed to make reduced glutathione.[76,77]

Speaking of increasing glutathione production and status, two of my clinical and well documented favorites are *N*-acetyl-L-cysteine (NAC) and acetyl-glutathione. Both are anti-inflammatory, antioxidant, heavy metal protectant, immunomodulatory, antiviral, neuroprotective and NAC acts as a mucolytic.[78,79,80,81,82]

Zinc, like vitamin C seems to be making headlines. A very important mineral in that it is needed for the normal development of the innate and adaptive immune systems.[83] It is antiviral via disruption of the viral life cycle and inhibits viral entry.[84,85] Even moderate deficiencies can increase the risk of opportunistic infections, including pneumonia.[86]

When most clinicians think of iodine/iodide, they think of thyroid. This mineral is also very important for proper immune function,[87] along with proper brain development.[88] The increased use of gourmet salts, guidelines for those with hypertension to limit salt intake, and the American diet tends to be low in sea vegetables, there of iodine induced goiter and hypothyroidism have become more prevalent.[89,90] The WHO estimates that over 30% of the world's population (about 2 billion people) have insufficient iodine intake.[91] It is essential for T4 and T3 production, highly concentrated in the thymus and needed for cell-mediated immunity by leukocyte myeloperoxidase.[86]

Edible (shiitake, maitake, oyster, lion's mane etc.) and non-edible medicinal mushrooms (reishi, turkey tail, cordyceps, chaga, etc.) while a staple in most Asian

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communities, are not viewed the in the same august manner in the United States. There is a reason why these creatures have their own biological kingdom. These are some of my favorite interventions with patients (and myself). There are dozens that have positive implications in human health and individually they are beyond the scope of this article, but generally their active constituents enhance immunity via increasing phagocytosis, increasing NK cell cytotoxicity, increasing T cell counts, and helping with Th1 phenotype potentiation.[92,93,94]

One of the most theorized mechanisms for which patients with severe SARS-CoV-2 decompensate and some unfortunately die, is possibly due to the "cytokine storm."[95,96] This is a process an overreaction to infection, leading to excessive and/or uncontrolled release of proinflammatory cytokines and immune system cells. Acute lung injury is a common consequence where local inflammation spills over into the systemic circulation, producing systemic sepsis.[97,98]

Given the seriousness of this, in my opinion, any intervention that may help *prevent* this from occurring, is a worthwhile endeavor, especially if those interventions are safe. Essential fatty acids (omega-3, 6 and 9), astaxanthin, green tea polyphenols, molecular hydrogen ($H_2$) are all well-established immunomodulatory and anti-inflammatory agents, that are also very safe.

Omega-3 (eicosapentaenoic acid, docosahexaenoic acid, Docosapentaenoic Acid), 6 (gamma linolenic acid) and 9 (oleic acid) can suppress NF-kB, COX-2, tumor necrosis factor (TNF)-α and IL-1-beta, modulate signal transduction, cell activation and cytokine production.[99,100,101]

*Camellia sinensis* (green tea) is high in polyphenols and catechins, which enhance cellular immune response, are antiviral and anti-inflammatory.[102,103,104,105,106,107]

*Haematococcus pluvialis* (astaxanthin) a carotenoid with potent antioxidant capabilities, may enhance antibody-mediated and cell-mediated immune responses.[108,109] A fascinating paper by Talukdar and others in April of 2020 provides a thorough discussion of how this molecule may attenuate cytokine storm.[110]

Molecular hydrogen is a diatomic molecule of hydrogen ($H_2$), the smallest known molecule, that is neutrally-charged, nonreactive, and nonpolar, which allows it to easily pass through cellular membranes and biological barriers. $H_2$ neutralizes hydroxyl radical (•OH)-a strong toxic oxidant-turns on antioxidant/detox enzymes and protein transcription via Nrf2 pathway, has anti-inflammatory effects, reducing pro-inflammatory cytokines like IL-1β, IL-6, TNF-α, and acts as a signaling molecule.[111,112]

## Treatment with Antiviral Compounds

My attempts below are not to recapitulate what has already been written, but rather discuss botanicals that I have successfully used clinically for the past ten years, have strong clinical studies are typically very safe, as well as some that haven't already been discussed in other publications.

Fucoidans are polysaccharide rich compounds (esp. polyphenols) in brown macroalgae. They have strong antioxidant properties, decrease IL-6, COX-1, COX-2 and LOX-15. They have been shown to increase NK cell activity, cytotoxic T cells, phagocyte activity and assist in dendritic cell maturation. These compounds also are antiviral by inhibiting viral entry into cell.[113,114,115]

Humic acid is an organic compound formed from decomposed plant materials and has been shown to be antiviral via binding to the virus, along with having immunostimulatory capabilities. Most of the data is in the herpes family of viruses, but I have seen it effective in those with other acute and chronic viral infections.[116,117,118,119]

Two of my favorite botanicals are *Astragalus membranaceus* (Huang Qi/Astragalus) and *Andrographis paniculata (*Andrographis), since they are strong antivirals and antimicrobials, they are immunomodulatory, anti-inflammatory and have adaptogenic properties. Andrographis has been shown to decrease inflammatory cytokines, prevent binding of viral hemagglutinin to cells, increase antibody activity and phagocytosis by macrophages.[120,121,122] Astragalus, like Andrographis, has been used by Eastern medical traditions (Chinese and Ayurveda) for thousands of years. It has been shown to be antiviral, increase IgG, IgA, IL-2, lymphocyte production and NK activity.[123,124,125]

The class of berberine alkaloids, which come from plants like *Berberis vulgaris, Berberis aristata, Mahonia aquifolium, Hydrastis canadensis* and others. They are anti-inflammatory, antioxidant, antimicrobial, antifungal, antiprotozoal, antimycobacterial and antiviral.[126,127,128,129,130] Caution at higher doses, since there may be some unwanted GI side effects (diarrhea, cramping, etc.).

Similar to the berberine containing genus of plants, the *Artemisia* genus has many species with medicinal properties. There are over 500 species in this genus,[131] comprising more than 839 chemical compounds.[132] The most famous species of the genus include *Artemisia annua* (Sweet Annie), *Artemisia vulgaris* (mugwort) and *Artemisia absinthium* (wormwood), with the most well-known constituents being artemisinin, artesunate, and dihydroartemisinin. These constituents have been well established to be antimicrobial, antimalarial, antifungal, and antiviral.[133,134,135,136,137]

Since the SARS-CoV-2 pandemic, *Sambucus nigra* (European elder/Black Elderberry) has become one of the most sought after botanicals and has also been in the press lately that it may elicit and/or exacerbate a "cytokine storm" in COVID-19 infected patients. This disseminated information was based upon one small 2001 *in vitro* study in which cytokines were released from leukocytes of healthy subjects.[138] On the contrary, a 2016 paper in *Phytomedicine* showed elderberry to have anti-cytokine properties.[139]

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There are three main medicinal parts of the plant: flowers, leaves and the berries.[140] The flowers and leaves have been used as a diaphoretic, diuretic, analgesic and anti-inflammatory. The bark and unripe berries and seeds contain cyanogenic glycosides which are toxic to humans. These parts of the plants must be adequately cooked to breakdown the cyanide.[141]

The berries, which are more medicinally well known, contain many flavonoids, but the most well studied include anthocyanidins, quercetin, rutin and isoquercetin.[142] They also contain phytosterols and carotenoids.[143] The polyphenols in the plant lend to its high antioxidant potential.[144]

The plant has anti-inflammatory, immunomodulatory and antiviral properties.[145,146] It has been shown in human studies to shorten the severity and duration of influenza,[147] and the common cold.[136,148]

*Pelargonium sidoides* (Umckaloabo) is a highly revered medicinal plant, native to South Africa. In recent years it has become popular here in the US, particularly in viral infections causing the common cold.[149,150] Medicinal constituents of the plant include coumarins, umckalin, catechin, gallocatechin, gallic acid ellagitannins, polyphenols, and proanthocyanidins.[151,152] These constituents allow the root of the plant to elicit antibacterial,[153] antiviral[153] and immunomodulatory affects.[154,155]

## Caveats

Some of the aforementioned interventions have a *relative* contraindication in autoimmune diseases, given that some may potentiate the immune system. Most of these cautions are theoretical but should not be taken without some level of caution. Assess the situation on a patient by patient basis. What I have found to be helpful is to pulse them, if going to be used long term, either few days on, few days off, or few weeks on, few weeks off. In this author's view and experience, short-term (3-10 days) use of these agents has been safe in autoimmune disease patients.

The content discussed in this article includes emerging nutritional science and scientific theories that should not be construed to be conclusive scientific proof of any specific cause, effect, or relationship, particularly when addressing COVID-19, since they have yet to be studied in this illness.

### References


1. None Listed. Microbiology by numbers. Nat Rev Microbiol. 2011 Sep;9(9):628. doi: 10.1038/nrmicro2644.
2. ViralZone. Human viruses and associated pathologies. SIB Swiss Institute of Bioinformatics. https://viralzone.expasy.org/678. Accessed Aug 14, 2020.
3. Sender R, Fuchs S, and Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol.* 2016 Aug 19;14(8):e1002533.
4. Mokili JL, Rohwer F, and Dutilh BE. Metagenomics and future perspectives in virus discovery. *Curr Opin Virol.* 2012 Feb;2(1):63-77.
5. Drexler, M. How Infection Works. "What You Need to Know About Infectious Diseases." National Academies Press (US); 2010. https://www.ncbi.nlm.nih.gov/books/NBK209710/. Accessed Aug 14, 2020.
6. Viruses. National Geographic Resource Library. https://www.nationalgeographic.org/encyclopedia/viruses/. Accessed Aug 14, 2020.
7. CDC. Influenza (Flu). The Flu Season. Last reviewed: July 12, 2018. https://www.cdc.gov/flu/about/season/flu-season.htm. Accessed Aug 14, 2020.
8. CDC. Common Cold. Last reviewed: March 18, 2019. https://www.cdc.gov/dotw/common-cold/index.html. Accessed Aug 14, 2020.
9. Kramer LD. Types of Viral Disorders. Merck Manual Professional Version. Last review March 2020. https://www.merckmanuals.com/professional/infectious-diseases/viruses/types-of-viral-disorders#v1017659. Accessed Aug 17, 2020.
10. Tesini BL. Coronaviruses and Acute Respiratory Syndromes (COVID-19, MERS, and SARS). Merck Manual Professional Version. Last review July 2020. https://www.merckmanuals.com/professional/infectious-diseases/respiratory-viruses/coronaviruses-and-acute-respiratory-syndromes-covid-19,-mers,-and-sars?query=coronavirus. Accessed Aug 17, 2020.
11. Johns Hopkins Corona Virus Resource Center. https://coronavirus.jhu.edu/map.html.
12. Lau H, T. Khosrawipour, P. Kocbach, et al. Evaluating the massive underreporting and undertesting of COVID-19 cases in multiple global epicenters. *Pulmonology*. 2020 Jun 6.
13. CDC Traveler's Health. COVID-19 in North Korea. Last reviewed August 6, 2020. https://wwwnc.cdc.gov/travel/notices/warning/coronavirus-north-korea. Accessed Aug 17, 2020.
14. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med*. 2020;382(12):1177. Epub 2020 Feb 19.
15. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672. Epub 2020 Apr 15.
16. CDC Coronavirus Disease 2019 (COVID-19). Symptoms of Coronavirus. Updated May 13, 2020. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed Aug 17, 2020.
17. Gillespe C. What's the Difference Between Asymptomatic and Presymptomatic Spread of COVID-19? Explore Health. June 11, 2020. https://www.health.com/condition/infectious-diseases/coronavirus/vaping-and-covid-19-risk. Accessed Aug 17, 2020.
18. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020;26(6):845. Epub 2020 Apr 29.
19. Deeks JJ, Dinnes J, Takwoingi, et al. Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev*. 2020;6:CD013652. Epub 2020 Jun 25.
20. Frellick M. 'Sweet Spot' for Antibody Tests is 3 to 4 Weeks Postexposure. Medscape Medical News. Aug 20, 2020. https://www.medscape.com/viewarticle/936084. Accessed Aug 21, 2020.
21. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. *N Engl J Med*. 2020 Jul 21;NEJMc2025179.
22. Long QX, Tang XJ, Shi Q, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat Med*. 2020;26(8):1200. Epub 2020 Jun 18.
23. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759. Epub 2020 Jun 19.
24. Mayo Clinic. Coronavirus Disease 2019 (COVID-19). Last updated Aug 7, 2020. https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963. Accessed Aug 14, 2020.
25. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054. Epub 2020 Mar 11.
26. Guan WY, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020.
27. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020.
28. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 - 24 February 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---24-february-2020. Accessed Aug 17, 2020.
29. Helleberg M, Niemann CU, Moestrup K, et al. Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. *J Infect Dis*. 2020 Jul 23;jiaa446.
30. CDC. Coronavirus Disease 2019 (COVID-19). Cleaning and Disinfection for Households. Updated July 10, 2020. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cleaning-disinfection.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fprepare%2Fcleaning-disinfection.html. Accessed Aug 17, 2020.
31. CDC. Coronavirus Disease 2019 (COVID-19). Social Distancing. Updated July 15, 2020. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/social-distancing.html. Accessed Aug 18, 2020.

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32. Segerstrom SC and Miller GE. Psychol Bull. 2004 Jul; 130(4): 601–630.
33. Olson EJ. Lack of sleep: Can It make you sick? Mayo Clinic. Nov. 28, 2018. https://www.mayoclinic.org/diseases-conditions/insomnia/expert-answers/lack-of-sleep/faq-20057757. Accessed Aug 18, 2020.
34. Winston D. Adaptogens: Herbs for Strength, Stamina, and Stress Relief. Healing Arts Press; 2nd Edition, Updated and Expanded edition (September 17, 2019).
35. Singh N, Bhalla M, Jager de P, et al. An overview on ashwagandha: a Rasayana (rejuvenator) of Ayurveda. *Afr J Tradit Complement Altern Med*. 2011;8(5 Suppl):208-213.
36. Whorwood CB, Sheppard MC, Stewart PM. Licorice inhibits 11 beta-hydroxysteroid dehydrogenase messenger ribonucleic acid levels and potentiates glucocorticoid hormone action. *Endocrinology*. 1993;132(6):2287-2292.
37. Anghelescu IG, Edwards D, Erich S. Stress management and the role of *Rhodiola rosea: a review. Int J Psychiatry Clin Pract. 2018 Nov;22(4):242-252.*
38. Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. *Altern Med Rev* 2000;5:334-46.
39. Pan L, Dong L, Juan L. Pharmacological perspective: glycyrrhizin may be an efficacious therapeutic agent for COVID-19. *Int J Antimicrob Agents*. 2020 Jun; 55(6): 105995. Published online 2020 Apr 24
40. Guizhi M , Wei L, Deqiang D, et al. Rhodiolosides A-E, monoterpene glycosides from Rhodiola rosea. *Chem Pharm Bull* (Tokyo). 2006 Aug;54(8):1229-33.
41. Kelly GS. Rhodiola rosea: a possible plant adaptogen. *Altern Med Rev* 2001;6:293-302.
42. Kim JY, Lee YJ. A Study on the Effects of Rhodiola rosea Root on the Immune System. *Korean J. of Herbology*. 2008;23(4):179-89.
43. Ferracioli-Oda E, Qawasmi A, Bloch MH. Meta-analysis: melatonin for the treatment of primary sleep disorders. *PLoS One*. 2013 May 17;8(5):e63773.
44. Reiter RJ, Calvo JR, Karbownik, M, et al. Melatonin and its relation to the immune system and inflammation. *Ann N.Y.Acad Sci* 2000;917:376-386.
45. Reiter RJ, Tan DX, Mayo JM, et al. Melatonin as an antioxidant: biochemical mechanisms and pathophysiological implications in humans. *Acta Biochim Pol.* 2003;50(4):1129-46.
46. Cardinali DP. High doses of melatonin as a potential therapeutic tool for the neurologic sequels of covid-19 infection. *Melatonin Res*. 2020, Vol 3 (3) 311-317.
47. Guerrero JM, Garcia-Mauriño S, Poz D, et al. Mechanisms Involved in the Immunomodulatory Effects of Melatonin on the Human Immune System. *The Pineal Gland and Cancer* 2001, pp 408-416.
48. Byrne A, Byrne DG. The effect of exercise on depression, anxiety and other mood states: a review. *J Psychosom Res*. 1993 Sep;37(6):565-74.
49. Pei-Yu Yang , Ka-Hou Ho, Hsi-Chung Chen, et al. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. *J Physiother*. 2012;58(3):157-63.
50. B K Pedersen, L Hoffman-Goetz. Exercise and the Immune System: Regulation, Integration, and Adaptation. *Physiol Rev*, 80 (3),1055-81 Jul 2000.
51. Calder PC. Feeding the immune system. *Proc Nutr Soc*. 2013 Aug;72(3):299-309.
52. Lazar V, Ditu LM, Pircalabioru GG, et al. Aspects of Gut Microbiota and Immune System Interactions in Infectious Diseases, Immunopathology, and Cancer. *Front Immunol*. 2018 Aug 15;9:1830.
53. Wu Hsin-Jung, Wu Eric. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes*. 2012 Jan 1; 3(1): 4–14.
54. Belkaid Y and Hand T. Role of the Microbiota in Immunity and inflammation. Cell. 2014 Mar 27; 157(1): 121–141.
55. Shokryazdan P, Jahromi FM, Navidshad B. Effects of prebiotics on immune system and cytokine expression. *Med Microbiol Immunol*. 2017 Feb;206(1):1-9.
56. E. P. Kiseleva. and G. I. Novik. Probiotics as immunomodulators: substances, mechanisms and therapeutic benefits. Microbial pathogens and strategies for combating them: science, technology and education (A. Méndez-Vilas, Ed.) 2013.
57. Gill H and Prasad J. Probiotics, Immunomodulation, and Health Benefits. *Adv Exp Med Biol* , 606, 423-54 2008.
58. Sam QH, et al. Immunomodulation as Therapy for Fungal Infection: Are We Closer? *Front Microbiol* , 9, 1612 2018 Jul 25.
59. Pothoulakis E. Review article: Anti-inflammatory mechanisms of action of *Saccharomyces boulardii. Aliment Pharmacol Ther*. 2009 Oct 15; 30(8): 826–833.
60. Clancy R. Immunobiotics and the probiotic evolution. *FEMS Immunol Med Microbiol*. 2003 Aug 18;38(1):9-12.
61. Hirose Y, et al. Oral intake of heat-killed Lactobacillus plantarum L-137 decreases the incidence of upper respiratory tract infection in healthy subjects with high levels of psychological stress. *J Nutr Sci*, 2, e39 2013 Dec 6 eCollection 2013.
62. Hirose Y, et al. Daily Intake of Heat-KilledLactobacillusplantarumL-137 Augments Acquired Immunity in Healthy Adults. *J Nutr*, 136 (12), 3069-73 Dec 2006.
63. Percopo CM, et al. Immunobiotic Lactobacillus Administered Post-Exposure Averts the Lethal Sequelae of Respiratory Virus Infection. *Antiviral Res*, 121, 109-19 Sep 2015.
64. Huang Z, et al. Role of Vitamin A in the Immune System. *J Clin Med*. 2018 Sep; 7(9): 258.
65. Roel M. van Harten, Esther van Woudenbergh, Albert van Dijk. Cathelicidins: Immunomodulatory Antimicrobials. *Vaccines* (Basel). 2018 Sep; 6(3): 63.
66. Aranow C. Vitamin D and the Immune System. *J Investig Med*. 2011 Aug; 59(6): 881–886.
67. Huang Z, et al. Role of Vitamin A in the Immune System. *J Clin Med*. 2018 Sep; 7(9): 258.
68. Mora JR, et al. Vitamin effects on the immune system: vitamins A and D take center stage. *Nat Rev Immunol*. 2008 Sep; 8(9): 685–698.
69. Gombart AF, et al. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. *Future Microbiol*. 2009 Nov;4(9):1151-65.
70. Erkurt MA, et al. Effects of cyanocobalamin on immunity in patients with pernicious anemia. *Med Princ Pract*. 2008;17(2):131-135.
71. Tamura J, et al. Immunomodulation by vitamin B12: augmentation of CD8+ T lymphocytes and natural killer (NK) cell activity in vitamin B12-deficient patients by methyl-B12 treatment. *Clin Exp Immunol*. 1999;116(1):28-32.
72. Yazdani Shaik BD and Conti P. Relationship between Vitamin C, Mast Cells and Inflammation. *J Nutr Sci*. 2016;6:456.
73. Hemilä H. Vitamin C and infections. *Nutrients*. 2017 Mar 29;9(4):339.
74. Carr AC, Maggini S. Vitamin C and immune function. *Nutrients*. 2017 Nov 3;9(11):1211.
75. Steinbrenner H, et al. Dietary selenium in adjuvant therapy of viral and bacterial infections. *Adv Nutr*. 2015 Jan 15;6(1):73-82.
76. Lubos E, Loscalzo J, Handy D. Glutathione Peroxidase-1 in Health and Disease: From Molecular Mechanisms to Therapeutic Opportunities. *Antioxid Redox Signal*. 2011 Oct 1; 15(7): 1957–1997.
77. Khomich OA, et al. Redox biology of respiratory viral infections. *Viruses*. 2018 Jul 26;10(8).
78. Kelly GS. Clinical applications of N-acetylcysteine. *Altern Med Rev* 1998;3:114-27.
79. Rahman, I, Adcock, I. M. Oxidative stress and redox regulation of lung inflammation in COPD. *Eur.Respir.J* 2006;28(1):219-242.
80. Geiler J, et al. N-acetyl-L-cysteine (NAC) Inhibits Virus Replication and Expression of Pro-Inflammatory Molecules in A549 Cells Infected With Highly Pathogenic H5N1 Influenza A Virus. *Biochem Pharmacol*, 79(3), 413-20 2010 Feb 1.
81. Bains JS, Shaw CA. Neurodegenerative disorders in humans: the role of glutathione in oxidative stress-mediated neuronal death. *Brain Res Rev*. 1997 Dec;25(3):335-58.
82. Sechi G, Deledda MG, Bua G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 1996 Oct;20(7):1159
83. Maares M & Haase H. Zinc and Immunity: An Essential Interrelation. *Arch Biocehm Biophys*. 2016 Dec 1. 611, 58-65.
84. Prasad AS. Zinc: mechanisms of host defense. *J Nutr*. 2007 May;137(5):1345-9.
85. Read SA, et al. The role of zinc in antiviral immunity. *Adv Nutr*. 2019 Jul 1;10(4):696-710.
86. Meydani SN, et al. Serum zinc and pneumonia in nursing home elderly. *Am J Clin Nutr*. 2007 Oct;86(4):1167-73.
87. Venturi S, Venturi M. Iodine, thymus, and immunity. *Nutrition*. 2009 Sep;25(9):977-9.
88. Delange F. The role of iodine in brain development. *Proc Nutr Soc*. 2000 Feb;59(1):75-9.
89. Dasgupta, Purnendu K, Yining Liu, et al. "Iodine nutrition: iodine content of iodized salt in the United States." *Environmental science & technology* 42.4 (2008): 1315-1323.
90. Krajčovičová-Kudláčková, M., et al. "Iodine deficiency in vegetarians and vegans." *Annals of nutrition and metabolism* 47.5 (2003): 183-185.
91. de Benoist B, McLean E, Andersson M, et al. Iodine deficiency in 2007: global progress since 2003. *Food Nutr Bull*. 2008;29(3):195-202.
92. Wang SY, et al. The anti-tumor effect of Ganoderma lucidum is mediated by cytokines released from activated macrophages and T lymphocytes. *Int J Cancer* 1997;70:699-705.
93. Tanaka A, et al. Enhancement of the Th1-phenotype immune system by the intake of Oyster mushroom (Tamogitake) extract in a double-blind, placebo-controlled study. *J Tradit Complement Med*. 2016 Oct; 6(4): 424–430.
94. Wu M, et al. Immunomodulatory properties of Grifola frondosa in submerged culture. *J Agric.Food Chem* 4-19-2006;54(8):2906-2914.
95. Ragab D, Eldin HS, Taeimah M, et al. The COVID-19 Cytokine Storm; What We Know So Far. *Front. Immunol.*, 16 June 2020.
96. Song P, Li W, Xie J, et al. Cytokine storm induced by SARS-CoV-2. *Clin Chim Acta*. 2020 Oct; 509: 280–287.
97. Acute lung injury (ALI) is a common consequence of a cytokine storm, where local inflammation spills over into the systemic circulation, producing systemic sepsis.

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98. Tisoncik JR, et al. Into the Eye of the Cytokine Storm. *Microbiol Mol Biol Rev*. 2012 Mar; 76(1): 16–32.
99. Kang JX & Weylandt KH. Modulation of inflammatory cytokines by omega-3 fatty acids. *Subcell Biochem*. 2008;49:133-43.
100. Chang CS, et al. Gamma-linolenic acid inhibits inflammatory responses by regulating NF-kappaB and AP-1 activation in lipopolysaccharide-induced RAW 264.7 macrophages. *Inflammation*. 2010 Feb;33(1):46-57.
101. Carrillo C, et al. Role of oleic acid in immune system; mechanism of action; a review. *Nutr Hosp*. 2012 Jul-Aug;27(4):978-90.
102. Kim YH, et al. Green tea catechin metabolites exert immunoregulatory effects on CD4(+) T cell and natural killer cell activities. *J Agric Food Chem*. 2016 May 11;64(18):3591-7.
103. Ide K, et al. Anti-influenza virus effects of catechins: a molecular and clinical review. *Curr Med Chem*. 2016;23(42):4773-83.
104. Steinmann J, et al. Anti-infective properties of epigallocatechin-3-gallate (EGCG), a component of green tea. *Br J Pharmacol*. 2013 Mar;168(5):1059-73.
105. Choi KC, Jung MG, Lee H, et al. Epigallocatechin-3-gallate, a histone acetyltransferase inhibitor, inhibits EBV-induced B lymphocyte transformation via suppression of RelA acetylation. *Cancer Res*. 1-15-2009;69(2):583-592.
106. Mohseni H, Zaslau S, McFadden D, et al. COX-2 inhibition demonstrates potent anti-proliferative effects on bladder cancer in vitro. *J Surg Res* 2004;119:138-42.
107. Ahmed S, Rahman A, Hasnain A, et al. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. *Free Radic Biol Med* 2002;33:1097-105.
108. Jyonouchi H, et al. Immunomodulating actions of carotenoids: enhancement of in vivo and in vitro antibody production to T-dependent antigens. *Nutr Cancer* 1994;21(1):47-58.
109. Park JS, et al. Astaxanthin decreased oxidative stress and inflammation and enhanced immune response in humans. *Nutr Metab* (Lond) 2010;7:18.
110. Talukdar, Jayanta, Dasgupta, et al. COVID-19: Potential of Microalgae Derived Natural Astaxanthin As Adjunctive Supplement in Alleviating Cytokine Storm (April 18, 2020). Available at SSRN: http://dx.doi.org/10.2139/ssrn.3579738
111. Ishibashi T. Molecular hydrogen: new antioxidant and anti-inflammatory therapy for rheumatoid arthritis and related diseases. *Curr Pharm Des*. 2013;19(35):6375-81.
112. LeBaron T, et al. Hydrogen gas: from clinical medicine to an emerging ergogenic molecule for sports athletes. *Can J Physiol Pharmacol*. 2019 Sep;97(9):797-807.
113. Araya, N, et al. Fucoidan therapy decreases the proviral load in patients with human T-lymphotropic virus type-1-associated neurological disease. *Antivir Ther*. 16(1): p. 89-98.
114. Myers, SP, et al. A combined Phase I and II open-label study on the immunomodulatory effects of seaweed extract nutrient complex. *Biologics*, 2011. 5: p. 45-60.
115. Hu Y, et al. Fucoidan enhances dendritic cell-mediated T-cell cytotoxicity against NY-ESO-1 expressing human cancer cells. *Biochem Biophys Res Commun* 2010.392:3, 329-34.
116. Klöcking R, Helbig B. Interaction of humic acids and humic-acid-like polymers with herpes simplex virus type 1. In: Allard B, Borén H, et al., eds. Humic Substances in the Aquatic and Terrestrial Environment. Lecture Notes in Earth Sciences, vol 33. Berlin and Heidelberg, Germany: Springer; 1991:407-12.
117. Klöcking R, Helbig B. Medical aspects and applications of humic substances. In: Steinbüchel A, Marchessault RH, eds. Biopolymers for Medical and Pharmaceutical Applications. Weinheim, Germany: WILEY-VCH Verlag GmbH & Co. KGaA; 2005:3-16.
118. Chen CH, et al. The effect of humic acid on the adhesibility of neutrophils. *Thromb Res* 2002;108:67-76.
119. Joone GK, et al. Investigation of the immunostimulatory properties of oxihumate. *Z Naturforsch* [C] 2003;58:263-7
120. Hu XY, et al. Andrographis paniculata (Chuan Xin Lián) for symptomatic relief of acute respiratory tract infections in adults and children: a systematic review and meta-analysis. *PLoS One* 2017;12(8):e0181780.
121. Burgos RA, et al. Efficacy of an Andrographis paniculata composition for the relief of rheumatoid arthritis symptoms: a prospective randomized placebo-controlled trial. *Clin Rheumatol*. 2009;28(8):931-946.
122. Puri A, et al. Immunostimulant agents from Andrographis paniculata. *J Nat Prod* 1993;56:995-9.
123. Yang, SP, et al. [Clinical effect of milkvetch extract oral liquid in preventing and treating children's recurrent respiratory tract infection]. Zhongguo Zhong.Xi.Yi.Jie.He.Za Zhi. 2008;28(6):544-547.
124. Sun Y, et al. Preliminary observations on the effects of the Chinese medicinal herbs Astragalus membranaceus and Ligustrum lucidum on lymphocyte blastogenic responses. *J Biol Response Mod* 1983;2:227-37.
125. Zhao, X. Z. [Effects of Astragalus membranaceus and Tripterygium hypoglancum on natural killer cell activity of peripheral blood mononuclear in systemic lupus erythematosus]. Zhongguo Zhong.Xi.Yi.Jie.He.Za Zhi. 1992;12(11):669-71, 645.
126. Ivanovska N, Philipov S. Study on the anti-inflammatory action of Berberis vulgaris root extract, alkaloid fractions and pure alkaloids. *Int J Immunopharmacol* 1996;18:553-61
127. Scazzocchio F, et al. Antibacterial activity of Hydrastis canadensis extract and its major isolated alkaloids. *Planta Med* 2001;67:561-4.
128. Sriwilaijareon, N, et al. Stage specificity of Plasmodium falciparum telomerase and its inhibition by berberine. Parasitol. Int 2002;51(1):99-103.
129. Zheng Li, et al. Antioxidant and Anti-Inflammatory Activities of Berberine in the Treatment of Diabetes Mellitus. *Evid Based Complement Alternat Med*, 2014, 289264.
130. Wu Y, et al. In Vivo and in Vitro Antiviral Effects of Berberine on Influenza Virus. *Chin J Integr Med*, 17(6), 444-52 Jun 2011.
131. José Abad M, Miguel Bedoya L, Bermejo P. Chapter 14 - Essential Oils from the Asteraceae Family Active against Multidrug-Resistant Bacteria. Fighting Multidrug Resistance with Herbal Extracts, Essential Oils and Their Components. 2013, Pages 205-221.
132. Koul B., Khatri T. (2020) The *Artemisia* Genus: Panacea to Several Maladies. In: Singh J., Meshram V., Gupta M. (eds) Bioactive Natural products in Drug Discovery. Springer, Singapore. https://doi.org/10.1007/978-981-15-1394-7_1
133. Juteau F, et al. Antibacterial and antioxidant activities of Artemisia annua essential oil. *Fitoterapia* 2002;73(6):532-535.
134. Bailey NJ, et al. Prediction of anti-plasmodial activity of Artemisia annua extracts: application of 1H NMR spectroscopy and chemometrics. *J Pharm Biomed Anal*. 4-1-2004;35(1):117-126.
135. Romero MR, et al. Antiviral effect of artemisinin from Artemisia annua against a model member of the Flaviviridae family, the bovine viral diarrhoea virus (BVDV). *Planta Med* 2006;72(13):1169-1174
136. Efferth T, et al. The Antiviral Activities of Artemisinin and Artesunate. *Clin Infect Dis*, 47 (6), 804-11 2008 Sep 15.
137. Vallès J, et al. Biology, Genome Evolution, Biotechnological Issues and Research Including Applied Perspectives in Artemisia (Asteraceae). *Advances in Botanical Research* 60:349-419.
138. Barak V, Halperin T and Kalickman I. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. *Eur Cytokine Netw*. 2001;12:290-296.
139. Kirichenko TB, Sobenin IA, Nikolic D, et al. Anti-cytokine therapy for prevention of atherosclerosis. *Phytomedicine*. 2016 Oct 15;23(11):1198-210.
140. European Medicines Agency. Assessment report on *Sambucus nigra L., fructus. Committee on Herbal Medicinal Products (HMPC). 28 January 2014.*
141. Ulbricht C, Basch E, Cheung L, et al. An evidence-based systematic review of elderberry and elderflower (Sambucus nigra) by the Natural Standard Research Collaboration. *J Diet Suppl*. 2014 Mar;11(1):80-120.
142. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the sambuci fructus effect and efficacy profiles. *Phytother Res*. 2010 Jan;24(1):1-8.
143. Vlachojannis JE, Cameron M, Chrubasik S. A systematic review on the sambuci fructus effect and efficacy profiles. *Phytother Res*. 2010 Jan;24(1):1-8.
144. Tiralongo E, Wee SS, Lea RA. Elderberry Supplementation Reduces Cold Duration and Symptoms in Air-Travellers: A Randomized, Double-Blind Placebo-Controlled Clinical Trial. *Nutrients*. 2016 Mar 24;8(4). pii: E182
145. Zakay-Rones Z, Thom E, Wollan T, Wadstein J. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res* 2004;32:132-40.
146. Porter RS and Bode R. A Review of the Antiviral Properties of Black Elder (Sambucus nigra L.) Products. *Phytother Res*. 2017 Apr;31(4):533-554.
147. Zakay-Rones, E Thom, T Wollan, et al. Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections. *J Int Med Res*. Mar-Apr 2004;32(2):132-40.
148. Hawkins J, Baker C, Cherry Lindsey, et al. Black elderberry (Sambucus nigra) supplementation effectively treats upper respiratory symptoms: A meta-analysis of randomized, controlled clinical trials. *Complement Ther Med*. 2019 Feb;42:361-365.
149. Lizogub VG, Riley DS, and Heger, M. Efficacy of a pelargonium sidoides preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial. *Explore*.(NY) 2007;3(6):573-584
150. Tahan F, Yaman M. Can the Pelargonium sidoides root extract EPs 7630 prevent asthma attacks during viral infections of the upper respiratory tract in children? *Phytomedicine* 2013;20(2):148-50.
151. Kolodziej H, Kayser O, Radtke OA, et al. Pharmacological profile of extracts of Pelargonium sidoides and their constituents. *Phytomedicine* 2003;10 Suppl 4:18-24.
152. Schotz K, Noldner M. Mass spectroscopic characterisation of oligomeric proanthocyanidins derived from an extract of Pelargonium sidoides roots (EPs 7630) and pharmacological screening in CNS models. *Phytomedicine* 2007;14 Suppl 6:32-9.